REMARKS

It is not believed that this response occasions any fee, but should there be any fee, please charge same to Deposit Account No. 10-9750/MCP0274/TT.

Claims 1 and 17-19 have been amended to affirmatively recite a particle size for the powdered wax. Support for this amendment can be found throughout the specification at, for example, page 4, lines 12-14 and original claim 16/

It is submitted that no new matter has been added by the above amendments.

Claims 1-20 are currently pending in the captioned application.

Obviousness Rejections

Claims 1-20 were rejected under 35 USC §103(a) as being unpatentable over by Cheng, US Patent No. 6,099,859 ("Cheng"), or Smith, US Patent No. 6,194,000 ("Smith"), or Harbit, US Patent No. 3,108,046 ("Harbit") in view of WO 01/21155 A1 ("Remon"). (Paper No. 11292005 at 2.)

For the reasons set forth below, the rejection, respectfully is traversed.

Cheng discloses

> [57] **ABSTRACT**
>
> A controlled release antihyperglycemic tablet that does not contain an expanding polymer and comprising a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane.
>
> SUMMARY OF THE INVENTION
>
> The foregoing objectives are met by a controlled release dosage form comprising:
>
> (a) a core comprising:
>
> (i) an antihyperglycemic drug;
>
> (ii) optionally a binding agent; and
>
> (iii) optionally an absorption enhancer;
>
> (b) a semipermeable membrane coating surrounding the core; and
>
> (c) at least one passageway in the semipermeable membrane.

The binding agent may be any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose, polymethacrylate, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent comprises approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core. Col 3

pharmaceutically acceptable water soluble polymer and the absorption enhancer is preferably formed by wet granulating the core ingredients and compressing the granules with the addition of a lubricant into a tablet on a rotary press. The core may also be formed by dry granulating the core ingredients and compressing the granules with the addition of a lubricant into tablets or by direct compression. Col. 4.

In an alternative embodiment, the dosage form of the present invention may also comprise an effective amount of the antihyperglycemic drug that is available for immediate release. The effective amount of antihyperglycemic drug for immediate release may be coated onto the semipermeable membrane of the dosage form or it may be incorporated into the semipermeable membrane.

In a preferred embodiment the dosage form will have the following composition:

	Preferred	Most Preferred
CORE:		
drug	50–98%	75–95%
binder	0–40%	3–15%
absorption enhancer	0–20%	2–10%
COATING:		
semipermeable polymer	50–99%	75–95%
flux enhancer	0–40%	2–20%
plasticizer	0–25%	2–15%

Col. 5

Smith discloses

(57) **ABSTRACT**

Disclosed is a method for the therapeutic treatment of pain related to wind up in a human or animal. The method of the invention is practiced by administering to the subject an effective amount of an analgesic pharmaceutical composition which includes a NMDA receptor antagonist in an immediate release form combined with an NMDA receptor antagonist in a sustained release form. The immediate release form and sustained release form are present in sufficient amounts to diminish or abolish wind up.

The formulation may include sufficient NMDA receptor antagonist to provide from about 1–5000 mg/day, typically 1–1000 mg/day and preferably about 100–800 mg/day of the active ingredient. The composition includes an NMDA receptor antagonist in an immediate release form in association with a NMDA receptor antagonist in a controlled release form. The composition may include an amount of NMDA receptor antagonist in the immediate release form of approximately 5% to 90% of the total NMDA receptor antagonist, preferably 10% to 60%. An immediate release NMDA receptor antagonist content of about 15% to 50% is particularly preferred. The controlled release form of the NMDA receptor antagonist may constitute the remainder of the active ingredients.

The composition of the invention may be in a form suitable for oral or rectal administration or for administration by transdermal, intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular means.

The composition of the invention may or may not be in a single dosage form. Preferably the composition is in a single dose form.

The composition may be formulated as an oral dosage form such as a tablet, capsule, a liquid, powder, granule or suspension, an injectable solution, a suppository, implant or transdermal patch.

Col. 2.

A suitable immediate release (IR) form of the NMDA receptor antagonist may simply be particles of the antagonist or particles of the antagonist admixed with soluble components for example, sugars (eg sucrose, lactose, fructose, mannitol etc.), polymers (eg polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc), surfactants (sodium lauryl sulphate, chremophor, tweens, spans, pluronics, and the like), insoluble components (microcrystalline cellulose, $Ca_3(PO_4)_2$, talc, fumed silica, i.e. aerosil® and the like), coating material (examples of suitable coating materials are polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids, etc.), dispersions in suitable material (examples are wax, polymers, pharmaceutically acceptable oils, soluble agents etc) or combinations of the above. These mixtures may be prepared by blending, mixing, dissolution and evaporation, or by using suspensions etc. These mixtures may be deposited on inert cores, wet massed and extruded, granulated, spray dried, etc. These mixtures or processed mixtures may be used in suspensions, filled into capsules, tabletted, filled into sachets, used in confectionery and so on.

Col. 3.

Harbit discloses

This invention relates to the method of making a high dosage sustained release orally administrable tablet and to the product of this method. More particularly, this invention provides a versatile, simplified method of preparing sustained release tablets with a high degree of control of the rate of drug release.

Col. 1

with poorly water soluble, high dosage drugs, thus permitting a higher dose of drug per tablet. Another advantage of this novel invention is that by spraying the wax on the granulation it is possible to utilize a positive, effective quantity of sustained release material thereby achieving the desired release rate with lesser quantities of wax, i.e., again making it possible to incorporate more drug in each tablet. In contrast to the approximately 30% minimum amount of sustained release material needed in the prior art sustained release tablets, the applicant can use a minimum amount of 2% and get ever release rates over a prolonged period of time.

Col. 2

In accordance with this invention the time delay material is a lipid material which is solid at room temperature, but has a low melting point of from 40° C. to 150° C. preferably 60° C. to 110° C. and is also nontoxic and pharmaceutically acceptable.

The time delay material is a substantially water insoluble material resistant to disintegration in the gastrointestinal tract and providing for a gradual release of the medicament in said tract. The time delay material may be, for example, a wax, a fatty acid, alcohol or ester, alone, or an admixture thereof.

The wax may be paraffin wax; a petrolatum wax; a mineral wax such as ozokerite, ceresin, utah wax or montan wax; a vegetable wax such as, for example, carnauba wax, Japan wax, bayberry wax, flax wax; an animal wax such as, for example, spermaceti; or an insect wax such as beeswax, Chinese wax or shellac wax.

Col. 3.

Remon discloses

(57) Abstract: Biologically inactive cushioning beads comprise at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least 30 % by weight of the biologically inactive cushioning beads. Such beads are useful for making solid shaped articles containing biologically active ingredients by compression.

The formulation of a solid oral dosage form, whether tablet or capsule, which disintegrates rapidly in water to form an instantaneous homogenous suspension of adequate viscosity to be swallowed could circumvent the problems of administering large dosages without premature release from controlled-release particles while providing a ready measured dose. The key to the development of such a dosage form is a rapidly disintegrating tablet which disperses to form a viscous suspension. A delay in the development of a viscous gel is essential for achieving disintegration of the tablet. On the

p. 1

properties.

The ideal solid oral dosage form should contain a swellable material which is able to increase viscosity on contact with water, at least one biologically active ingredient for immediate or sustained release delivery of the biologically active ingredient, and a filler conferring compactibility and the capability to disintegrate quickly. The inclusion of a viscosity increasing agent as a fine powder in the tablet matrix without any processing would interfere with disintegration and result in the formation of a voluminous hydrophilic mass which is impossible to disperse. Thus, it is necessary to incorporate such an agent into the tablet as granules or spheres so that the disintegration process occurs before the viscosity increase.

p. 2

The present invention may provide biologically inactive cushioning beads comprising at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least about 30% by weight of the biologically inactive cushioning beads and which are useful for making solid shaped articles containing biologically active ingredients by compression.

p. 10

For the performance of the present invention, it is preferable to use a microcrystalline hydrocarbon wax having a congealing point between about 50°C and 90°C and which is water-insoluble. The microcrystalline hydrocarbon wax usually comprises a mixture of linear (normal) and branched (iso) hydrocarbons, According to a preferred embodiment of the present invention, the said mixture comprises from about 30 to about 90% by weight of linear hydrocarbons and from about 10 to about 70% by weight of branched hydrocarbons. Also preferably, the microcrystalline hydrocarbon wax

p. 12

flavoring agent (e.g. vanillin), buffering agent, filler, disintegrating agent and/or swellable material. Preferably the cushioning beads of the present invention include at least about 5% by weight of at least one such biologically inactive pharmaceutically acceptable additive (excipient) distributed throughout the beads, for instance in the form of an intimate mixture of wax and excipient. A disintegrating agent is especially useful as an excipient for providing quick-disintegrating characteristics when making a solid shaped article containing biologically active ingredients by compression.

p. 15

In making the rejection as to Cheng, the Examiner asserted that

> Cheng teaches a controlled release oral tablet comprising from 75-95% drug and up to about 40% waxes (see column 3, lines 34-49; and column 5, lines 30-36). The tablet provides both, immediate release and controlled release (see column 5, lines 22-26). The tablet further comprises fatty acid, surfactant (flow aid), and chelating agent (column 3, lines 51-60), and can further be coated with a semi-permeable membrane comprises cellulose derivatives polymer (see column 4, lines 11-44). Cheng also discloses the tablet is prepared by compression (see column 6, lines 35-41).

(Paper No. 11292005 at 2)

As to Smith, the Examiner further asserted that

> Smith teaches an analgesic composition comprising immediate and controlled release forms (see abstract). The immediate release comprises up to 90% of the analgesic agent, polyethylene glycol, waxes, and other carriers (column 2, lines 39-50; and column 3, lines 29-51). The dosage form provides from about 1-5000 mg/day of the analgesic agent (ID). The composition is in for oral administration in tablet or capsule or granule form (column 2, lines 55-67). Suitable coating to provide sustained release comprises cellulose derivatives polymer (column 4, lines 26-45).

(*Id.* at 2-3)

As to Harbit, the Examiner asserted that:

> Harbit teaches a high dose tablet comprising from about 75% to about 98% drug and wax, such as paraffin wax or shellac wax (column 3, lines 1-31). The tablet dosage further comprises lubricant (column 4, lines 9-19). The dosage form provides both immediate release and sustained release (column 4, lines 21-31).

(*Id.* at 3.)

The Examiner acknowledged, however, that "the references do not explicitly teach wax in powder form.. (*Id.* at 3.)

To fill the acknowledged gap, the Examiner relied upon Remon. The Examiner contended that

- "Remon teaches a rapidly disintegrating tablet comprising an active agent and wax particles." (*Id.*)
- The wax is a microcrystalline wax or a natural wax. (*Id.*)
- The "composition further contains disintegrants, swellable materials as well as other fillers." (*Id.*)
- The wax particles have an average particle size of 0.5 to 2.0 mm. (*Id.*)
- The actives are chosen from a wide variety of known pharmaceutical agents. (*Id.*)
- The composition includes a film coating. (*Id.*)
- The tablets are produced by compression. (*Id.*)
- The tablets are rapid disintegration tablets. (*Id.*)

The Examiner admitted that "Remon does not refer to wax particles as powder." (*Id.*) To fill this acknowledged gap, the Examiner looked to a dictionary definition for powder ("any solid, dry material of extremely small particle size."). Based on that definition the Examiner merely concluded that "it would have been obvious to one of ordinary skill in the art to modify the composition of Cheng, or Robinson, or Smtih using the wax in view of the teaching of Remon, because Remon teaches tablet compression suitable in pharmaceutical art." (*Id.*)

The Examiner stated further

> Regarding claim 16, Remon does not expressly teach the same particle size for the wax particles. However, at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to vary particles sizes in tablet formulations. It is the position of the Examiner that this is limitation that would be routinely determined by one of ordinary skill in the art, through minimal experimentation, as being suitable, absent the presentation of some unusual and/or unexpected results. The results must be those that accrue from the specific limitations. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the ad at the time the invention was made.

(*Id.* at 4)

Examiner Repeats Rejection but Fails Again to provide Basis for Rejection

This is the second paper in a row where the Examiner stated that Harbit formed the basis for an obviousness rejection and **again** there is no conclusion or reasoning of obviousness based on Harbit provided by the Examiner for which a response can be provided. For this reason the rejection based on Harbit is improper and should be withdrawn.

Record Contains Factual Inaccuracies

Obviousness ***must*** be based upon facts, "cold hard facts." When a conclusion of obviousness is not based upon facts, it cannot stand.

1) In setting forth the factual basis for the instant rejection the Examiner asserted that Remon discloses, among other things, "**wax particles**." (Paper No. 11292005 at 3.) The following passages were affirmatively relied on by the Examiner for this factual assertion:

> **The present invention may provide biologically inactive cushioning beads comprising at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least about 30% by weight of the biologically inactive cushioning beads and which are useful for making solid shaped articles containing biologically active ingredients by compression.**

(Remon, p. 10, lns. 14-18.)

by the extrudate density and granulating fluid content.

In view of their properties, the cushioning beads such as disclosed above are useful for, among others, producing by compaction a wide range of solid shaped articles of biologically or therapeutically active ingredients. Thus a second object of the present invention consists of a solid shaped article containing biologically active ingredient-loaded beads and further comprising biologically inactive cushioning beads comprising at least one compressible cushioning component consisting essentially of a microcrystalline hydrocarbon wax or a natural wax, the said wax being at least about 30% by weight of the biologically inactive cushioning beads.

The term "solid shaped article " as used herein means any article being in a hard solid state at temperatures not exceeding about 60°C and having a definite geometrical shape, such as for instance ordinary tablets, effervescent tablets, multilayer tablets, sustained-release tablets, pills, lozenges and other compressed dosage forms.

(Remon, p. 19, lns. 10-21.

However, it is not seen the above passages where **wax particles** are disclsoed. Remon discloses **cushioning beads**. The record in this case does not contain any facts that support the proposition that **cushioning beads** are the same as **wax particles**. Nor is it seen where Remon recites the term "particle" these passages, much less the term "wax particles." The Examiner failed to make the requested showing as to where the term "wax particles" is used in Remon. Because the rejection is based on an apparent mischaracterization of the factual disclosure of Remon that has not been addressed by the Examiner after being requested to do so, the rejection is improper and should be withdrawn.

2) Further, the Examiner opines that "the average size of the **wax particles** is from 0.5 to 2.0 mm." The following is the passage at page 18, lines 7-18, relied on by the Examiner for this factual assertion:

> The cushioning beads of the present invention preferably have an average particle size of about 0.5 to about 2.0 mm and most preferably from 0.75 to 1.25 mm. They can be produced by a number of different techniques such as high-shear mixing, extrusion, extrusion-spheronization or by other means, as long as the said technique results in free-flowing beads, not granules, having a narrow size distribution range. The preferred production process involves high-shear mixing of the microcrystalline hydrocarbon wax or natural wax of similar characteristics and the optional additives (excipients) in view to achieve the average particle size mentioned above. As used herein, the term "high-shear mixing " means mixing the beads components at a high shear rate as is readily known to those skilled in the art. When high-shear mixing is used as the production technique, the temperature of mixing and should preferably be in the range of about 45 to about 60°C, most preferably in the range of about 50 to about 55°C.

As is seen above, the passage is directed to "**cushioning beads**." According to Remon, the cushioning beads are made of additional materials besides wax. The following passage from page 15. lines 9-20, support this fact.

> In addition to the microcrystalline hydrocarbon wax or natural wax of substantially similar characteristics, the cushioning beads of the present invention may include up to about 70% by weight of another compressible biologically inactive cushioning component or at least a biologically inactive but pharmaceutically acceptable additive (excipient) such as colorant, sweetener (e.g. sucrose, mannitol, saccharin and aspartame), flavoring agent (e.g. vanillin), buffering agent, filler, disintegrating agent and/or swellable material. Preferably the cushioning beads of the present invention include at least about 5% by weight of at least one such biologically inactive pharmaceutically acceptable additive (excipient) distributed throughout the beads, for instance in the form of an intimate mixture of wax and excipient. A disintegrating agent is especially useful as an excipient for providing quick-disintegrating characteristics when making a solid shaped article containing biologically active ingredients by compression.

Therefore, "the average size of the **wax particles**" relied on by the Examiner is actually for the **cushioning beads**, not for individual **wax particles**. In addition, the cushioning beads can include other ingredients, which could influence the size of the cushioning beads. For this reason, the factual basis for the rejection appears to be improper, which renders the rejection improper for this additional reason. The rejection should be withdrawn.

Examiner Appears To Be Using Hindsight Reconstruction

A determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor.

In making the instant rejections, the Examiner admitted that Cheng or Smith or Harbit do not teach wax in powder form. The Examiner used Remon to fill this gap. However, the Examiner admitted that Remon does not refer to the wax particles as powder or teach the same particle size for the wax particles as found in claim 16. The Examiner used extrinsic evidence to fill the gaps left by Remon, namely Kornhaber and Mueller. The documents were used to demonstrate that microcrystalline wax has a particle size in the range of either about 2.5 microns to about 500 nm or about 1 micron to about 300 microns.

The Examiner appears to be reconstructing the claimed invention based on the impermissible use of hindsight. The amended claims affirmatively require a particle size for the wax powder. There is no suggestion or disclosure in Remon as to the particle size of the microcrystalline wax (we know there are at least two different particle size types of microcrystalline wax based on Kornhaber and Mueller). Yet Remon does not provide any motivation let alone any disclosure of the particular particle size of the microcrystalline was used therein. Nor does Remon disclose any particle particle size for the natural wax disclosed therein. For this additional reason, the rejection is improper and should be withdrawn.

Rejections Do not Provide Requisite Specificity

A *prima facie* case of obviousness, however, requires that the rejection describe with specificity **why** one skilled in the art would have combined two references to arrive at the claimed invention. In the present case, no such explanation is found in the rejections. The Examiner merely concluded that 1) "it would have been obvious for one of ordinary skill in the art to modify the composition of Cheng, or Smith, using the wax in view of Remon because Remon teaches tablet composition suitable in the

pharmaceutical art" and "it would have been obvious to a person of ordinary skill in the art to vary particle sizes." (Paper No. 11292005 at 4.) Yet there are no reasons provided as to why one of ordinary skill in the art would vary particle sizes, much less use the claimed wax powder. Thus, the rejection is not supported by the kind of specificity required to sustain a conclusion of obviousness.

Rejection as to Cheng in view of Remon

For a *prima facie* case of obviousness to be established, the teachings from the prior art itself must appear to have suggested the claimed subject matter to one of ordinary skill in the art. The mere fact that the prior art could be modified as proposed by the Examiner is not sufficient to establish a *prima facie* case of obviousness.

As to claim 5, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of water-soluble, non-saccharide polymeric binders" is disclosed or suggested by Cheng. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 6, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of hydrated polymers" is disclosed or suggested by Cheng. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 18, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of water-soluble, non-saccharide polymeric binders" is disclosed or suggested by Cheng. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 19, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of hydrated polymers" is disclosed or suggested by Cheng. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 20, the Examiner failed to state where the affirmatively required disclosure of an "active ingredient is in its native crystalline form is disclosed or

suggested by Cheng. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

Even further, the rejection does not point out where there is a disclosure or a suggestion of the required powdered wax in a swallowable immediate release tablet and a swallowable immediate release tablet meeting the USP dissolution specifications for immediate release tablets containing said active ingredient. For these further reasons, the rejection is improper and should be withdrawn.

Rejection as to Smith in view of Remon

For a *prima facie* case of obviousness to be established, the teachings from the prior art itself must appear to have suggested the claimed subject matter to one of ordinary skill in the art. The mere fact that the prior art could be modified as proposed by the Examiner is not sufficient to establish a *prima facie* case of obviousness.

As to claim 5, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of water-soluble, non-saccharide polymeric binders" is disclosed or suggested by Smith. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 6, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of hydrated polymers" is disclosed or suggested by Smith. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 18, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of water-soluble, non-saccharide polymeric binders" is disclosed or suggested by Smith. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 19, the Examiner failed to state where the affirmatively required disclosure of a "tablet [that] is substantially free of hydrated polymers is disclosed or suggested by Smith. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

As to claim 20, the Examiner failed to state where the affirmatively required disclosure of an "active ingredient is in its native crystalline form" is disclosed or suggested by Smith. Nor is it seen where Remon fills this gap. Because the Examiner failed to satisfy the minimum burden, the rejection is improper and should be withdrawn.

Even further, the rejection does not point out where there is a disclosure of the required powdered wax in a swallowable immediate release tablet and a swallowable immediate release tablet meeting the USP dissolution specifications for immediate release tablets containing said active ingredient. For this additional reason, the rejection is improper and should be withdrawn.

Finally, the Examiner is invited to call the applicants' undersigned representative if any further action will expedite the prosecution of the application or if the Examiner has any suggestions or questions concerning the application or the present Response. In fact, if the claims of the application are not believed to be in full condition for allowance, for any reason, the applicants respectfully request the constructive assistance and suggestions of the Examiner in drafting one or more acceptable claims pursuant to MPEP §707.07(j) or in making constructive suggestions pursuant to MPEP §706.03 so that the application can be placed in allowable condition as soon as possible and without the need for further proceedings.

Respectfully submitted,

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